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Parenteral Cephalosporin Therapy in Ambulatory Care

Advantages and Disadvantages

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Abstract

Outpatient parenteral antibiotic therapy (OPAT) programmes are effective, well tolerated and economically advantageous in carefully selected patient populations. Inclusion criteria for patient selection for OPAT include good clinical appearance and uncomplicated infection. By virtue of their favourable microbiological and pharmacological properties, cephalosporins in general, and ceftriaxone in particular, are the most widely prescribed antibiotics for OPAT worldwide.

OPAT was largely created to prolong parenteral therapy following early discharge and has now been extended to community general practice. Indeed, more than 250 000 treatments are performed in the US each year for a wide variety of serious infections, with an increase of 100% during the last 5 years.

In 1994, an advisory committee was created in Canada to provide guidelines for home intravenous therapy. Of the 3 models that were defined (the visiting nurse model, the infusion centre model and the self-administration model), the OPAT self-administration model offers considerable cost savings and is probably largely utilised in a number of countries, such as Italy, where specific models have not been codified.

Once the need for parenteral antibiotic therapy has been established, the choice of antibiotic is the second step in the decision-making process. Third generation cephalosporins are characterised by a number of important advantages in the OPAT setting, namely a favourable antibacterial spectrum, tolerability profile and patient compliance, as well as advantageous cost considerations.

While the advantages of parenteral cephalosporin therapy in the ambulatory care setting outweigh the disadvantages in terms of cost effectiveness and rapid onset of action, adverse events such as pain at the injection site following intramuscular administration and phlebitis after intravenous infusion should be borne in mind.

Whenever antimicrobial therapy is to be initiated a number of factors have to be considered, including choice of antibiotic, route of administration, dosage, daily number of administrations, duration of therapy and cost. The route of administration is often the first step in deciding to use antimicrobial therapy and it can, in some instances, dictate the choice of antibiotic.

Different pharmaceutical formulations of antibiotics are commercially available for oral administration (tablets, suspensions, liquid), and for parenteral administration (vial with or without li-

docaine) for intramuscular or intravenous treatment.

The choice of a parenteral route of administration is determined by 3 different factors, i.e. impaired gastrointestinal absorption, nonavailability of oral antibiotics and severity of the disease. The first 2 factors can be considered as an 'absolute' indication for parenteral therapy and cannot be modified.

The main causes of impaired gastrointestinal absorption of oral antibiotics are diarrhoea, nausea or vomiting, gastrectomy and short bowel syndrome, while the main classes of antibiotics with no oral formulations available are aminoglycosides, carbapenems and glycopeptides. The use of parenteral drugs in these cases is obvious.

The severity of the disease as a factor affecting the choice of administration route is more difficult to define. Several standard criteria have been adopted to classify the severity of infections, but still no real correlation is possible between the severity of the disease and the route of administration to be chosen.[1]

Nevertheless, parenteral administration is usually reserved for more severe diseases, as intravenous antibiotics (and to a lesser extent intramuscular antibiotics) are believed to guarantee prompt and high serum levels, which the oral route cannot always ensure.

Fig. 1. National projections by country from survey data of routes of administration of antibiotics (reprinted from Halls,[2] with permission of Oxford University Press).

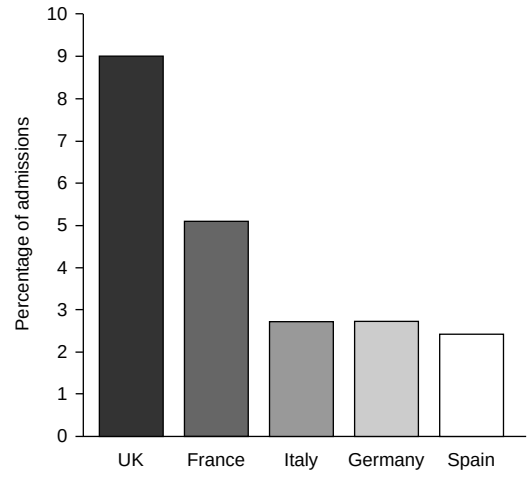

Fig. 2. Percentage of patients admitted to hospital by the European general practitioners' survey of decisions (adapted from Schaberg et al.,[3] with permission of the BMJ Publishing Group).

The choice of parenteral administration for more severe diseases remains an individual and empirical decision and is generally associated with hospitalisation.

The above-mentioned considerations only partly comply with the data reported by Halls and Schaberg et al.[2,3] (figs 1 and 2). Indeed, both the decision to hospitalise and the choice of parenteral antibiotic administration for hospitalised patients vary greatly in different European countries. These variations probably reflect different 'rules and habits' regarding the use of parenteral antibiotics, which, in turn, affect the prescribing behaviour of general practitioners (GPs) in different countries (table I).

Table II and figure 3 show the results of a survey of parenteral antibiotic prescriptions and recourse to complementary diagnostic procedures by a number of European GPs.[4]

It is interesting that Italian and French GPs very frequently utilise the parenteral route of administration for the treatment of lower respiratory tract infections (LRTI), while in Germany and the UK

Table I. Rules and 'habits' regarding the use of injectable antibiotics in different countries

UK	GP can prescribe, but does not usually do so
	At the Home Care Centres, injections can be given by GP or nurse only
	Antibiotic and sanitary costs are reimbursable
France	GP can prescribe
	Injections can be given by GP or nurse; both GP and nurse costs are refundable
Germany	GP can prescribe
	Injections can be administered only by GP
	GP has a limited budget for pharmaceutical expenses, but not for complementary diagnostic procedures
Italy	GP can prescribe
	Intravenous injections can be given only by GP, even at the patient's home
	Intramuscular antibiotic can be self-administered
USA	GP can prescribe
	Antibiotics can be self-administered
	Healthcare insurances refund antibiotic and doctor or nurse expenses

GP = general practitioner.

this route is very seldom used, and complementary diagnostic procedures are more frequently carried out in Germany. Both these trends can be explained by the tendency of GPs in Italy and France to prescribe parenteral antibiotics as opposed to oral formulations, and to carry out antibiotic treatment outside the hospital setting.

1. Outpatient Parenteral Antibiotic Therapy

In the early 1980s in the US, the advantages (such as reduced cost, no hospitalisation trauma in children, no 'immobilisation syndrome' in the elderly, and reduction of nosocomial and acquired infections by multiresistant organisms) of outpatient parenteral antibiotic therapy (OPAT) were identified and suitable therapeutic programmes were established.

Several different OPAT models have been developed in the US, but the OPAT team is generally, as suggested by Tice,[5,6] made up of 3 different professionals, i.e. physicians, nurses and pharmacists, each of whom has their own specific responsibility. The physician is, of course, responsible for establishing the diagnosis and authorising the treatment, or, in other words, is responsible for the patient selection, which is a fundamental issue for OPAT. Patients, in fact, must be accurately selected according to different clinical and social criteria, which have been clearly identified by Fine[7] for outpatient therapy of pneumonia but which can, in our opinion, be generalised for other diagnoses.

Inclusion criteria for patient selection for OPAT are good clinical appearance and uncomplicated infection, while exclusion criteria consist of poor clinical appearance, high risk aetiology, concomitant disease (e.g. diabetes, congestive heart failure, renal insufficiency), immunosuppression, poor social support and poor patient reliability.

OPAT was created mainly to prolong parenteral therapy after early discharge and is now extended to the community general practice. More than 250 000 treatments are performed each year in the US for many different serious diseases, with an increase of 100% in the last 5 years. Infections currently amenable to OPAT are listed in table III.[8,9]

1.1 Guidelines for Home Intravenous Therapy

After the US experience of OPAT a few other countries have, more recently, set up their own OPAT programmes. According to data from the

Table II. Parenteral administration of antibiotics in the community setting in different European countries (% of prescriptions) [adapted from Houchon et al.,[4] with permission]

Country	Community-acquired pneumonia (%)	Acute bronchitis (%)	Exacerbation of chronic bronchitis (%)	All infections (%)
France	17	7	22	15.3
Germany	6	0	0	2
Italy	71	47	58	58.6
Spain	15	5	11	10.3
UK	0	0	1.2	0.4

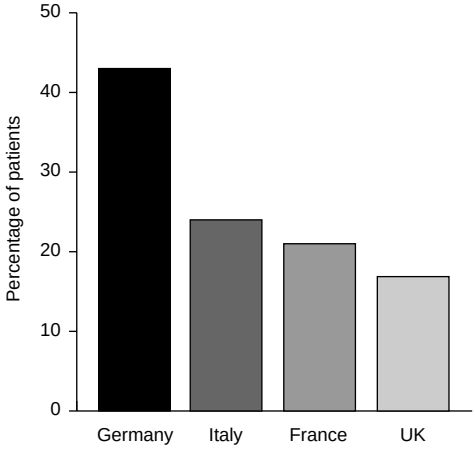

Fig. 3. Recourse to complementary diagnostic procedures by European general practitioners (GPs).

international scientific literature, OPAT programmes have already been created in the US, Canada, The Netherlands, the UK, Australia and Israel.[5] In 1994, for example, an advisory committee was created in Canada to set the guidelines for home intravenous therapy.[10] Three different models were defined: (i) the visiting nurse model; (ii) the infusion centre model; and (iii) the self-administration model.

As reported at the Consensus Conference in Toronto, Canada, 11 to 12 November 1994, 'the OPAT self-administration model is the preferred delivery model if patients are willing and able to participate. This model offers considerable cost saving, particularly for prolonged courses of treatment, in that the overhead and personnel costs are both considerably reduced'.[10]

This model is particularly interesting, and it is probably largely utilised in some other countries (e.g. Italy) where specific models have not been codified.

Considering the consumption of injectable antibiotics outside the hospital environment in some European countries, the use of parenteral drugs is surprisingly high in Italy and France.[11] Regarding the use of injectable antibiotics, there is, at least in Italy, broad consensus by patients for different cultural reasons. This makes the 'OPAT Italian model' unique and accounts for 19% (10 042 000 of 53 390 000) of the total injectable antibiotic prescriptions in 1996.[11]

2. Serious Infections Amenable to OPAT

As previously reported in table III, several serious infections can be treated with parenteral antibiotics in the outpatient setting.

2.1 Endocarditis

There are an estimated 5000 to 8000 new cases of endocarditis in the US each year. It frequently occurs in patients with pre-existing heart diseases, but also in intravenous drug abusers and patients undergoing cardiac surgery. The aetiology of endocarditis varies greatly according to the risk factors involved. Endocarditis in patients with rheumatic valve disease is usually associated with a streptococcal aetiology, with the exception of enterococcus. It is usually an uncomplicated infection, patients have a good clinical picture and streptococci are usually sensitive to β-lactam antibiotics. Consequently, the clinical and aetiological patterns of streptococcal endocarditis make it amenable to OPAT.

Three different studies on the efficacy of OPAT in patients with streptococcal endocarditis have been reported.[12-14] Patients received a partial course (early discharge) or the whole course of parenteral antibiotic therapy in the outpatient setting. Ceftriaxone was administered intra-

Table III. Infections amenable to outpatient parenteral antibiotic therapy

Lower respiratory tract infections
Abscesses
Cellulitis
Endocarditis
Exacerbation of chronic obstructive pulmonary disease
Meningitis
Pelvic inflammatory disease
Pyelonephritis
Osteomyelitis
Septic arthritis

venously or intramuscularly at a dosage of 1 to 2g once a day or in combination with gentamicin (5 mg/kg/day) for 2 to 4 weeks, with or without a subsequent course of oral amoxicillin (1g 4 times daily) for 2 weeks. All the studies reported that the therapy was well tolerated and effective and that ceftriaxone was appropriate for OPAT of streptococcal endocarditis.

2.2 Bacterial Meningitis

Bacterial meningitis is a serious infection that mostly occurs in paediatric patients. Approximately 90% of paediatric bacterial meningitis is caused by *Neisseria meningitidis*, *Haemophilus influenzae* or *Streptococcus pneumoniae*, which are all sensitive to β-lactam antibiotics. Children with bacterial meningitis are good candidates for early discharge and prolonging intravenous antibiotic therapy at home. These patients should be hospitalised to initiate intravenous antibiotic therapy with a second or third generation cephalosporin (ceftriaxone or cefotaxime), which are characterised by a high penetration into CSF, in combination with or without dexamethasone. The patient can be discharged if there are no neurological complications, the clinical response to therapy is good and the patient is persistently afebrile for 24 to 48 hours.

Bradley[15] reported a favourable clinical outcome for 24 children with *H. influenzae* meningitis who benefited from OPAT after an early discharge. All patients had been treated with ceftriaxone at a dose of 80 mg/kg given intravenously once a day.

2.3 Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is the most frequent consequence of sexually transmitted disease (STD) in young women, but its real incidence has not been ascertained, as declaring it is not obligatory. This makes it difficult to carry out an epidemiological survey. Its incidence in the US is probably more than 1 000 000 cases per year, but only 250 000 women per year who suffer from PID are hospitalised. It is therefore presumed that many PID patients utilise an OPAT programme according to the Centers for Disease Control recommendations, which advise the use of injectable second or third generation cephalosporins as first-line antibiotic regimens.[16]

2.4 Osteomyelitis and Septic Arthritis

Osteomyelitis and septic arthritis are particularly well suited to OPAT. These infections require prolonged treatment (from 4 to 6 weeks) and the benefits offered by OPAT and early discharge are obvious.

Until a few years ago osteomyelitis was one of the most frequent disorders treated in the US under OPAT programmes.[17,18] Osteomyelitis and septic arthritis are most commonly caused by pathogens such as *Staphylococcus aureus*, *S. epidermidis*, *H. influenzae* and *Streptococcus* spp. These pathogens are sensitive to β-lactam antibiotics such as cephalosporins, which offer excellent penetration into the bone tissue. However, more recently, the use of fluoroquinolones and third generation oral cephalosporins seems to be preferable, and this has limited the use of parenteral antibiotics for these infections.[19]

2.5 Bacterial Pneumonia and Exacerbation of Chronic Obstructive Pulmonary Disease

Bacterial pneumonia and exacerbation of chronic obstructive pulmonary disease (COPD) are the most frequent community-acquired infections that require parenteral antibiotic therapy. Community-acquired pneumonia (CAP) is generally caused by *S. pneumoniae* and, to a lesser extent, by *H. influenzae* and *Moraxella (Branhamella) catarrhalis*. Penicillins and cephalosporins are the most suitable antibiotics for the treatment of this disease under an empirical regimen, despite the high incidence of penicillin resistant *S. pneumoniae* in some countries, e.g. France, Hungary, Spain and South Africa.[20,21]

Atypical pathogens such as *Mycoplasma* and *Chlamydia* are less frequently responsible for CAP and are more difficult to identify. Atypical pneumonia can be managed with oral or parenteral macrolides.

Trowbridge[22] reported that, of 1006 patients treated for lower respiratory tract infection, more than half received an OPAT course with ceftriaxone or, less often, ceftazidime, because of the high activity of these antibiotics against the above-mentioned pathogens and their simplicity of administration.

Exacerbation of COPD can also benefit from OPAT. Penicillin and cephalosporin derivatives are still the most suitable antibiotics to be used in this situation. Kuzemko and Strandvik[23,24] provided a useful therapeutic insight in 2 well documented groups of patients with exacerbation of COPD and cystic fibrosis. Since *Pseudomonas* is most often the responsible pathogen in cystic fibrosis, patients were treated with an aminoglycoside plus a broad spectrum penicillin or cephalosporin.

3. Choice of Antibiotic in OPAT

Once the need for parenteral antibiotic therapy has been established, the choice of the antibiotic will be the second step in the decision-making process. The OPAT National Programmes do not give any recommendations for the use of specific antibiotics, as the choice of antibiotic in the outpatient setting is part of the individual therapeutic programme. This choice is obviously determined, in the case of nonmicrobiologically documented infection, by the most probable aetiological agent responsible for the infection to be treated, but important factors in addition to the antimicrobial spectrum of the drug should be taken into account. These include tolerability, compliance and the cost of the antibiotics.

Table IV. Anti-infective agents used in 957 patients with various infections treated with 1115 antimicrobial drugs (adapted from Williams,[25] with permission from Elsevier Science)

Antimicrobial agent	No. (%)
Third generation cephalosporins	341 (30.6)
First and second generation cephalosporins	279 (25)
Penicillins	165 (14.8)
Aminoglycosides	115 (10.3)
Vancomycin	88 (7.9)
Other anti-infectives	127 (11.4)

Table V. Infections treated and antibiotics used in the outpatient parenteral antibiotic therapy team programme in 1993 in Tacoma, Washington (adapted from Tice,[26] with permission)

	No. of patients
Infection	
Skin/soft tissue	236
Osteomyelitis	102
Joint infections	43
Gynaecological infections	35
Ear-nose-throat infections	25
Bacteraemia	14
Pulmonary infections	12
Other	71
Total	**538**
Antibiotic	
Ceftriaxone	292
Vancomycin	113
Cefazolin	44
Clindamycin	42
Ceftazidime	39
Oxacillin	36
Tobramycin	28
Gentamicin	29
Other	112
Total	**735**

Even though data reported till now suggest that β-lactam antibiotics, and especially cephalosporins, are the most frequently utilised antibiotics in OPAT, it is not easy to quantify from the OPAT literature what proportion of diagnoses are treated in the outpatient setting and what antibiotics are used.

Data published recently by Williams and Tice[25,26] provide some useful information. Williams[25] in his retrospective study outlined the use of anti-infective drugs in 957 antibiotic courses (table IV). The author did not provide data concerning the antibiotic used by diagnosis. Tice reported the diagnosis and treatment of 538 patients with various infections treated in 1993 in a private institute in Tacoma, Washington (table V). Ambulatory treatment of these infections led to a remarkable saving in terms of costs and a noticeable improvement in their patients' quality of life.

Further information concerning the choice of antibiotic for OPAT comes from the paediatric

Table VI. Prescriptions for cephalosporins outside the hospital setting in 1996 in Italy

Antibiotic	Units (no. of prescriptions)	Percentage
Total antibiotics	53 390 000	100
Total orals	43 348 000	81
Total injectables	10 042 000	19
Ceftriaxone	2 016 000	42
Cefodizime	807 000	17
Ceftazidime	783 000	16
Cefotaxime	666 000	14
Others	533 000	11

setting. Dagan et al.[27] reported excellent results in 55 paediatric patients treated entirely at home for infections localised at different sites (cellulitis, mastoiditis, pneumonia, urinary tract infection and others). All patients were treated with ceftriaxone given once a day for 5 to 12 days.

In an outpatient setting between 1983 and 1990, ceftriaxone was administered to 200 paediatric patients with different documented infections caused by pathogens sensitive to ceftriaxone. The drug was always given once a day, intravenously or intramuscularly (mostly intramuscularly), and the clinical outcome was always favourable.[28]

Most of the information concerning the use of antibiotics outside the hospital is provided, in my opinion, by the Italian market.[29] Table VI shows the prescriptions for cephalosporins outside the hospital setting in Italy in 1996. Third generation cephalosporins accounted for approximately half of the market of injectable antibiotics.

Although these data concern a well-defined geographical area and the previously described OPAT Italian model is quite atypical, it is evident that cephalosporins (and ceftriaxone in particular) are the most widely used parenteral antibiotics.

Tables VII and VIII provide further data concerning injectable antibiotic prescriptions by age and diagnosis in Italy. It is evident that Italian GPs treat a wide range of infections according to OPAT programmes, especially infections of the lower respiratory tract. The use of injectable antibiotics for upper respiratory tract infection (9.4% of the market) was surprising, but it was also surprising that no children in any other country demonstrated any intolerance (such as vomiting or diarrhoea) to oral antibiotics, which would make it necessary to switch from oral to parenteral therapy.

3.1 Advantages of Cephalosporins in OPAT

What then are the reasons for the success of cephalosporins in general, and ceftriaxone in particular, which make them the most prescribed antibiotics for OPAT worldwide? As already mentioned in section 3, the factors that strongly influence the choice of antibiotic are antibacterial spectrum, tolerability, compliance and cost.

3.1.1 Antibacterial Spectrum

The antibacterial spectrum of third generation cephalosporins covers most of the pathogens responsible for community-acquired infections, and bacterial resistance due to selective pressure has not arisen even in Italy, despite its wide use of these antibiotics in community practice.[30,31]

3.1.2 Tolerability

Tolerability is largely demonstrated by the use of several millions of antibiotic courses in hospitals and community settings for the widest range of infections.[32] Third generation cephalosporins do not usually require laboratory monitoring, although for infectious diseases most practitioners

Table VII. Prescription analysis by diagnosis in Italy in 1996

Diagnosis	Percentage of prescriptions	
	oral antibiotics	injectable antibiotics
URTI	27	9
LRTI	16	48
UTI	11	6
Otitis/mastoiditis	5	3
Other	41	34

LRTI = lower respiratory tract infection; **UTI** = urinary tract infection; **URTI** = upper respiratory tract infection.

Table VIII. Injectable antibiotic prescriptions by age in Italy in 1996. Data are expressed as percentages

	Age (years)		
	0-11	12-54	>55
All injectable antibiotics	7	43	50
Third generation cephalosporins	9	40	51

Table IX. Acquisition costs [in Italian lire (L)] of some injectable antibiotics in Italy 1997

Intramuscular drug	Daily dose	Acquisition cost per vial (L)	Daily cost for therapy (L)
Ceftriaxone (1g)	1g × 1	28 600	28 600
Cefotaxime (1g)	1g × 3	14 200	42 600
Ceftizoxime (1g)	1g × 3	16 200	48 600
Ceftazidime (1g)	1g × 3	24 600	79 200
Piperacillin (2g)	2g × 3	15 700	47 100
Cefazolin (1g)	1g × 3	8 000	24 000
Cefuroxime (1g)	1g × 3	8 800	26 400
Cefotetan (1g)	1g × 2	24 500	49 000
Cefoxitin (1g)	1g × 3	12 400	37 200

with experience in OPAT suggest a weekly test for BUN/creatinine and AST to evaluate renal and liver function.[33]

3.1.3 Compliance

Compliance with OPAT is obviously related to the daily number of administrations needed for a correct therapy, which depends on the pharmacokinetic and pharmacodynamic characteristics of the antibiotic (e.g. postantibiotic effect, protein binding, serum half-life). Serum half-life is probably the main pharmacokinetic parameter affecting the number of doses to be given per day. According to the serum half-life, ceftriaxone is the only cephalosporin that can be given once a day; cefonicid, cefotetan and cefodizime can be administered twice a day, and all the others are given 3 times a day (or twice a day if given intramuscularly). It is obvious that antibiotics such as ceftriaxone, which, with a single administration guarantee the same therapeutic efficacy as other antibiotics, will be favoured as the therapy of choice.

3.1.4 Cost Considerations

The economic advantages of OPAT are also evident and many studies have clearly demonstrated these advantages in terms of direct and indirect cost savings.[34,35] The main reason for the self-administration model being largely utilised in Italy, and increasingly in the US and other countries, is probably the direct cost of acquiring the antibiotics. Table IX presents the direct costs of the most commonly used cephalosporins. As seen from the table, ceftriaxone remains the most advantageous cephalosporin in this regard.

Capri recently compared the total cost for the treatment of LRTI in an Italian hospital setting with the outpatient setting following the self-administration Italian model.[36] He considered 2 cost hypotheses, the minimum and the maximum, according to the cost of antibiotic chosen and the duration of therapy (table X). He calculated that, with the budget provided by the National Health Service for the treatment of a patient with LRTI (table XI), from 6 to 25 patients could be treated at home. In other words, with the same amount of money needed for treating 100 patients at home with OPAT, we could treat only 3 to 4 patients in the hospital setting.

3.2 Disadvantages of Cephalosporins in OPAT

Although it is clear that the advantages of parenteral cephalosporins in the ambulatory care setting are greater than the disadvantages in terms of

Table X. Cost [in Italian lire (L)] of ambulatory parenteral therapy in Italy for lower respiratory tract infection

Lower cost hypothesis	L302 500
Less expensive third generation cephalosporin	
5 days' therapy	
L75 000 for medical and nurse expenses	
Higher cost hypothesis	L871 000
Most expensive third generation cephalosporin	
10 days' therapy	
L150 000 for medical and nurse expenses	

Table XI. Total cost [in Italian lire (L)] for lower respiratory tract infection in the hospital setting in Italy in 1994

Diagnosis-related group	No. of cases	Cost (L thousands)	Total cost (L billions)
Exacerbation of COPD	109 983	5104	569
Complicated pneumonia	27 660	6969	191
Pneumonia with pleuritis	53 003	5128	268
Noncomplicated pneumonia	20 248	3357	64

COPD = chronic obstructive pulmonary disease.

cost effectiveness, tolerability and compliance, a few disadvantages should be highlighted. These include rare anaphylactic reactions that can occur with the first dose or delayed allergic reactions during long term treatments. Other adverse advents such as leucopenia or renal toxicity, which are not infrequent after weeks of treatment, or adverse effects due to inappropriate administration of the drug (electrolyte imbalance or arrhythmias), can be observed,[37,38] in addition to pain at the injection site following intramuscular administration[39] and a small incidence of phlebitis after intravenous infusion.[40]

The incidence of these disadvantages can be greatly reduced by the accurate selection, education and training of the patient, who must be aware of all the possible adverse effects and complications that can occur at different stages of short or prolonged antibiotic parenteral treatment.

4. Conclusion

In conclusion, OPAT in selected patients is effective, well tolerated and economically advantageous. Cephalosporins in general, and ceftriaxone in particular, are the most widely used antibiotics for OPAT worldwide because of their microbiological and pharmacological characteristics.

In many countries, OPAT programmes are under development, and many others are looking with interest to the Italian OPAT model and choice of antibiotic.

Increasing the number of OPAT programmes by accurately selecting those patients who can avoid hospitalisation is probably advantageous. However, it is also necessary to avoid overuse by carefully selecting the patient for parenteral therapy or oral antimicrobial therapy.

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